CASE REPORTS

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Anhidrotic Ectodermal Dysplasia with Frequent Infections and Amyloidosis

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ANHIDROTIC ECTODERMAL DYSPLASIA is an X-linked recessive disorder in which affected males lack eccrine sweat glands and teeth, and have heat intolerance, sparse hair and a characteristic facies.[1] This condition has long been recognized, reports including a note by Charles Darwin[2] about the "toothless men of Sind": ten men in four generations in one Hindu family in Hyderabad, India, with unaffected women transmitting the disorder to their sons and with no instance of fathers transmitting the disorder to their sons. In fact, carrier females often show patchy signs of the disease such as absent or malformed teeth, irregular sweating and breast abnormalities. Expression in females is due to the phenomenon of random inactivation of the X chromosome, so that some cells express the normal gene carried on one X chromosome and others express the gene for ectodermal dysplasia carried on the other chromosome.[3,4]

The frequent occurrence of atrophic rhinitis, pharyngitis, bronchitis and pneumonia noted in affected males has been attributed to scanty mucus production and deficient ciliary action in the upper respiratory tract.[1,5,6] Additional factors, such as allergic asthma, cigarette smoking and occupational dust exposure have been implicated in some cases.[1,6,7] Cutaneous infections have not been noted in these reports.

We describe here a patient with X-linked ectodermal dysplasia and frequent cutaneous and respiratory infections, in whom certain aspects of host defense mechanisms were investigated. This case is unique in having amyloidosis and nephrotic syndrome as a complication.

Report of a Case

The index case (III-27, see Figure 1) is a 44-year-old unemployed chemist with anhidrotic ectodermal dysplasia, recurrent infections and nephrotic syndrome due to amyloidosis. The family history (see pedigree, Figure 1) shows

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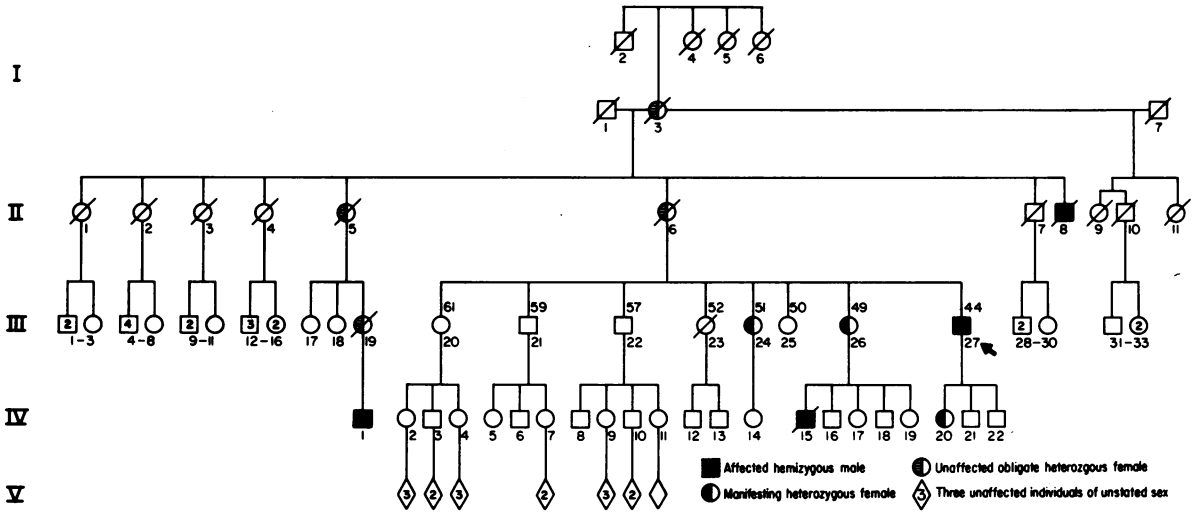

Figure 1.—Family pedigree showing typical X-linked pattern of transmission. Arrow indicates patient.

typical X-linked recessive inheritance of ectodermal dysplasia with four involved males and at least seven carrier females, three of whom have partial expression of the disease. The involved second cousin (IV-1) of the propositus was evaluated at the University of Washington Hospital in 1960 at age 21; in addition to the typical physical features of anhidrotic ectodermal dysplasia, he had allergic asthma with acute bronchospasm, recurrent pulmonary and upper respiratory infections with an acute left lower lobe pneumonia, and esophageal stenosis requiring repeated dilatation. The involved nephew (IV-15) and uncle (II-8) of the propositus were said to have frequent pulmonary infections and rhinitis. The daughter (IV-20) and one known carrier sister (III-26) of the propositus had abnormal "razorlike" teeth. Another sister (III-24) had nearly the full syndrome with sparse hair, anodontia, saddle nose deformity and anhidrosis except for scattered small patches of skin which exhibited normal sweating. She has also had recurrent respiratory infections. An additional sister (III-23) without signs of ectodermal dysplasia died at age 52 of chronic renal failure following a long history of rheumatoid arthritis.

In the propositus, recurrent purulent and atrophic rhinitis have been present since childhood. Pneumonia occurred at ages 12 and 20 and recurred several times between ages 20 and 35. Recurrent cutaneous infections began at about age 30. Over the past ten years of observation at the University of Washington Affiliated Hospitals, the following infections have been documented: November 1965—right upper lobe pneumonia; July 1966—left arm cellulitis and abscess; November 1970—cellulitis of nose following attempted surgical correction of saddle nose deformity with spread to left orbit; December 1970—herpes zoster around left eye with staphylococcal superinfection; February 1971—left shoulder cellulitis and abscess; November 1971—right middle lobe pneumonia; January 1972—superinfection of chemical burns on thighs; January 1972—bacterial cellulitis complicating third degree thermal burn on hand; November 1972—severe periorbital edema with cellulitis; November 1972—thigh abscess; December 1972—right upper lobe pneumonia; June 1973—leg ulcers infected with staphylococci; August 1973—thigh abscess; January 1975—infected leg ulcers; March 1975—right middle lobe pneumonia. The cases of pneumonia were characterized by fever, leukocytosis, pulmonary infiltrates, dyspnea and cough, but sputum production was scanty probably due to the absence of mucus glands. Sputum cultures were often not helpful, although Streptococcus pneumoniae and Hemophilus influenzae were isolated on some occasions. Pulmonary function tests done when the patient was not infected were normal. Staphylococcus aureus was cultured from cutaneous infections in nearly all instances; these responded to appropriate antibiotics, drainage and local therapy. The infections have frequently arisen in association with trauma including surgical operation, burns and self-administered parenteral medication.

Drug abuse has been a problem for 10 to 15 years and includes both oral and subcutaneous administration. Codeine and pentazocine have been the most frequently used agents, but barbiturates, meprobamate, glutethimide, chloral hydrate and methadone have been taken intermittently. Frequent psychiatric problems have arisen in relation to the drug usage. The patient is of normal or higher intelligence and is well educated. Before the drug abuse began he was a successful businessman and chemist.

Results on physical examinations when the patient has been free of infections have shown only the characteristic manifestations of anhidrotic ectodermal dysplasia, including sparse scalp and body hair, anhidrosis, depressed nasal bridge, prominent forehead, defective dentition with only a single peg-shaped tooth and normal fingernails and toenails.

Findings on analysis of urine and on serum protein determinations were normal until November 1972 when periorbital and lower extremity edema developed. Analysis of urine showed 3+ protein, but findings were otherwise normal and a 24-hour urine protein value was 5 grams. Creatinine clearance was 100 ml per minute; blood urea nitrogen (BUN), 14 mg per 100 ml; serum albumin, 2.5 grams per 100 ml and cholesterol 228 mg per 100 ml. Results on intravenous pyelogram were normal. Tests for rheumatoid factor and antinuclear antibodies were negative. A percutaneous renal biopsy (January 1972) showed extensive amyloid deposition. All glomeruli were hypocellular and distorted by large amorphous eosinophilic deposits in the mesangial regions, extending peripherally to obliterate the capillary lumens. These deposits stained metachromatically with crystal violet and were birefringent with congo red. Smaller deposits were

identified in the interstitium and in arterial and arteriolar walls. Amyloid fibrils were shown by electron microscopy (Figure 2). Treatment with furosemide, 40 to 240 mg per day, was partially successful in controlling edema. The proteinuria and hypoalbuminemia have persisted at about the same level. Hypertension (160/100) together with azotemia (creatinine, 3.3 mg per 100 ml; BUN, 61 mg per 100 ml) developed in May 1975.

Evaluation of Host Defense

Studies of host defense mechanisms are summarized in Table 1. Serum levels of immunoglobulins G, M and E were normal and IgA was somewhat elevated. Serum complement levels (total hemolytic activity and C3 by immunodiffusion) were normal. Blood leukocyte counts and differential counts were normal as was the morphology of blood and bone marrow leukocytes. Neutrophil myeloperoxidase was normal by a cytochemical technique employing benzidine.[8] Neutrophil chemotaxis was evaluated by a previously reported method[9] employing ^{51}Cr-labeled neutrophils and a standard chemotactic factor (human C5a). The response of the neutrophils was equivalent to that of normal neutrophils. Generation of serum chemotactic activity by endotoxin activation[9] was also normal. Neutrophil iodination was studied by a modification of a previously described method.[10] The reaction mixture contained normal serum, zymosan as the phagocytic particle, ^{125}I and either normal or patient neutrophils. The normal response observed indicated intact phagocytosis, metabolic activity and myeloperoxidase activity. T-lymphocyte function was not evaluated, although the spectrum of infectious agents observed in the patient does not suggest an abnormality in this area.

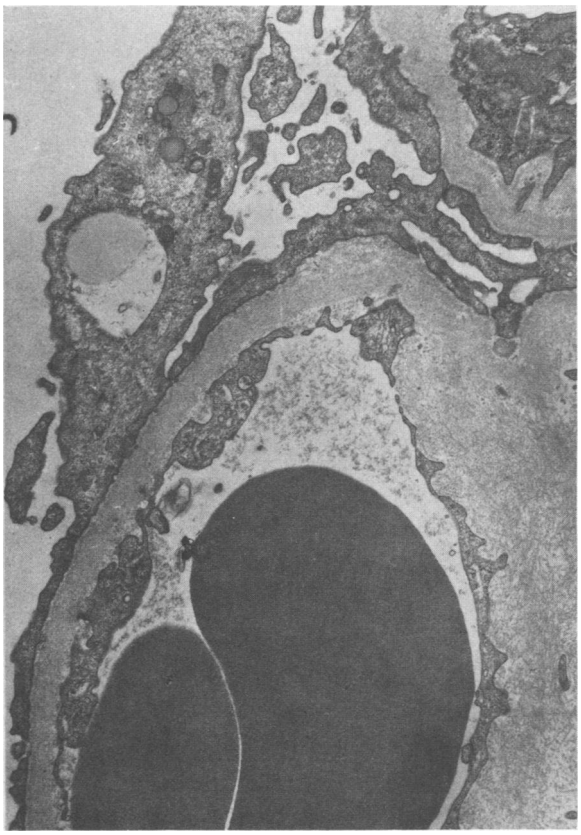

Figure 2.—Electron micrograph of a peripheral glomerular capillary loop. The foot processes are fused. There is a small mass of fibrils on the epithelial aspect of the glomerular basal lamina and in the adjacent subendothelial region. The largest mass of fibrils can be seen on the right. These fibrils have the size, distribution and location of amyloid fibrils. X22,400. (Micrograph provided by Dr. Gary R. Striker)

Discussion

In the patient reported here there is a typical family history, physical examination and clinical history for X-linked anhidrotic ectodermal dysplasia. Although most reported cases have been in infants and children, numerous adults are known with this disorder, having survived with great care to avoid high environmental temperatures and to control high fevers. The unusual features of this case are the numerous and varied infections and the eventual development of amyloidosis and nephrotic syndrome.

There is no history of allergic asthma or occupational dust exposure, in this patient, but some of the infections, particularly the episodes of cellulitis, were clearly related to subcutaneous self-

TABLE 1—*Studies of Host Defense Mechanisms**

Test	*Patient*	*Normal*
Immunoglobulins		
IgG (mg/100 ml)	1600	600-1700
IgA (mg/100 ml)	640	50-300
IgM (mg/100 ml)	140	50-200
IgE (U/ml)	128	25-300
Complement		
CH_{50} (units)	142	80-162
C3 (mg/100 ml)	165	120-170
Neutrophil Function		
Myeloperoxidase	Present	Present
Chemotaxis†	..	..
Cell response	101.5%	>70%
Serum activity	73.3%	>70%
Iodination‡	73.9	40-80

*See text for methods and explanations.
†Percent of normal control.
‡Nmoles/10^7 cells/hour.

administration of drugs. He was not known to have injected agents intravenously. No abnormalities in neutrophil function or levels of serum complement or immunoglobulins were detected. The patient's infections appear most likely related to local factors such as the abnormal epidermal and epithelial barrier rather than to a systemic defect in phagocytic or immune mechanisms. Although frequent respiratory infections have been noted in other patients with anhidrotic ectodermal dysplasia,[1,5,6] the occurrence of multiple cutaneous infections has not been described.

Amyloidosis with nephrotic syndrome is a recognized complication of chronic inflammatory conditions including dermatoses. In a review of 100 cases of systemic amyloidosis, eight were associated with cutaneous disorders.[11] The dermatoses included hidradenitis suppurativa, stasis ulcers of 25 years' standing, psoriatic arthritis, recurrent basal cell carcinoma, dystrophic epidermolysis bullosa and three cases of lepromatous leprosy.

The patient's family history is interesting because of the examples of partial expression in female carriers. In fact, one sister has all of the major manifestations of anhidrotic ectodermal dysplasia. The development in another sister of renal failure in association with chronic rheumatoid arthritis raises the interesting possibility of amyloidosis in another family member, although medical records could not be obtained for confirmation.

Summary

A patient is described with anhidrotic ectodermal dysplasia, frequent cutaneous and respiratory infections and amyloidosis with nephrotic syndrome. The increased susceptibility to infections appeared to be related primarily to local factors since phagocytic and immune function were intact. Amyloidosis, a previously unreported complication of anhidrotic ectodermal dysplasia, probably developed as a consequence of the recurrent infections.

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Osteogenesis Imperfecta Tarda

Cardiovascular Pathology

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OSTEOGENESIS IMPERFECTA TARDA is a rare inherited disorder of connective tissue characterized by skeletal, ocular, cutaneous, otologic, dental and internal abnormalities. It is related to such conditions as Marfan's syndrome and pseudoxanthoma elasticum. In contrast to the other inherited disorders of connective tissue, valvular heart disease has rarely been documented by cardiac catheterization in patients with osteogenesis imperfecta tarda. In McKusick's review of more than 100 cases of osteogenesis imperfecta tarda, two patients were judged to have aortic regurgitation on clinical grounds.[1] Criscitiello and co-workers in 1965 reported the cases of three patients with aortic regurgitation.[2] Cardiac catheterizations were not done although one case came to postmortem examination. Recently, five cases of valvular heart disease in patients with osteogenesis imperfecta tarda have been evaluated in the cardiac catheterization laboratory.[3-5] In three patients aortic regur-

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large.

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